Neural Crest Cell Implantation Restores Enteric Nervous System Function and Alters the Gastrointestinal Transcriptome in Human Tissue-Engineered Small Intestine.

Journal: Stem Cell Reports

Publication Year: 2017

Authors: Christopher R Schlieve, Kathryn L Fowler, Matthew Thornton, Sha Huang, Ibrahim Hajjali, Xiaogang Hou, Brendan Grubbs, Jason R Spence, Tracy C Grikscheit

PubMed link: 28803915

Funding Grants: Mechanism of Tissue Engineered Small Intestine Formation, The generation and expansion of tissue-engineered small intestine from human stem/ progenitor cells: a preclinical study of functional translation, ASCENT- Advanced Stem Cell Enteric Neuropathy Therapy

Public Summary:
Acquired or congenital disruption in enteric nervous system (ENS) development or function can lead to significant mechanical dysmotility. ENS restoration through cellular transplantation may provide a cure for enteric neuropathies. We have previously generated human pluripotent stem cell (hPSC)-derived tissue-engineered small intestine (TESI) from human intestinal organoids (HIOs). However, HIO-TESI fails to develop an ENS. The purpose of our study is to restore ENS components derived exclusively from hPSCs in HIO-TESI. hPSC-derived enteric neural crest cell (ENCC) supplementation of HIO-TESI establishes submucosal and myenteric ganglia, repopulates various subclasses of neurons, and restores neuroepithelial connections and neuron-dependent contractility and relaxation in ENCC-HIO-TESI. RNA sequencing identified differentially expressed genes involved in neurogenesis, gliogenesis, gastrointestinal tract development, and differentiated epithelial cell types when ENS elements are restored during in vivo development of HIO-TESI. Our findings validate an effective approach to restoring hPSC-derived ENS components in HIO-TESI and may implicate their potential for the treatment of enteric neuropathies.

Scientific Abstract:
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